Importance of blood glucose management in the multifactorial approach of absolute cardiovascular risk in type 2 diabetes: the lessons from the Steno 2 Study

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A B S T R A C T

The problem of blood glucose as a cardiovascular risk factor has long been debated. Indeed, increasing arguments confirm the importance of blood glucose on cardiovascular risk, as shown by the results from epidemiological studies and therapeutic investigations. However, the literature has demonstrated the importance of postprandial blood glucose, or post-load-glucose, on cardiovascular risk. One could think that blood glucose, in particular postprandial blood glucose, is an independent, although not major, cardiovascular risk factor compared to other classical risk factors such as hypercholesterolemia, high blood pressure, and smoking, but it potentiates the risk when it coexists with these classical risk factors. This explains the increased prevalence of cardiovascular morbi-mortality in diabetic patients, in particular type 2 diabetes. Multifactorial treatment can reduce the cardiovascular risk by 55%, as the Steno 2 study demonstrated.

Key-words: Blood glucose · Postprandial glycemia · Cardiovascular risk · Type 2 diabetes · Intensive therapy.

Résumé

Poids de la gestion des facteurs glycémiques dans l’approche multifactorielle du risque cardiovasculaire absolu du diabète de type 2 : les leçons de l’étude Steno 2

Depuis longtemps, le problème de la glycémie en tant que facteur de risque cardiovasculaire indépendant, est débattu. En fait, de plus en plus d’arguments confirment le poids de la glycémie sur le risque cardiovasculaire, d’après les résultats d’études d’abord épidémiologiques, puis d’interventions thérapeutiques. Cependant, la littérature met en évidence le poids de la glycémie postprandiale, ou de la glycémie postcharge orale en glucose, sur le risque cardiovasculaire. L’on peut penser que la glycémie, et en particulier postprandiale, est un facteur de risque cardiovasculaire indépendant, non majeur, comparativement aux autres facteurs de risque classiques comme l’hypercholestérolémie, l’hyper-tension artérielle et le tabagisme, mais elle potentialise le risque, lorsqu’elle coexiste avec ces facteurs de risque classiques. Cela explique la prévalence accrue de morbi-mortalité cardiovasculaire chez le patient diabétique, en particulier de type 2. Une prise en charge multifactorielle permet de réduire le risque cardiovasculaire de 55 %, comme l’a montré l’étude Steno 2.

Mots-clés : Glycémie · Glycémie postprandiale · Risque cardiovasculaire · Diabète de type 2 · Traitement intensif.
Blood glucose is an independent cardiovascular risk factor. In 1991, the Framingham Heart Study confirmed that blood glucose was an independent risk factor after multivariate analysis and adjustment for other cardiovascular risk factors [1]. In 1993, the MRFIT (Multiple Risk Factor Intervention Trial) showed that the risk of cardiovascular mortality increased in a linear fashion depending on the number of classical risk factors such as smoking, hypercholesterolemia, or systolic hypertension [2]. However, when the diabetic population is separated from the nondiabetic population, the authors observed that the diabetes systematically potentiated the risk, independently of the number of risk factors at inclusion. Even more important, the risk persisted in diabetic subjects who presented no other classical risk factor. This study confirmed that hyperglycemia is an independent risk factor, although not a major one, of cardiovascular mortality in type 2 diabetes subjects. However, hyperglycemia greatly potentiates the other classical risk factors.

The studies published by Haffner et al. in 1998 [3] and Malmberg et al. in 2000 [4] confirmed that every diabetic patient without coronary disease should be treated as if he were virtually afflicted with coronary heart disease.

In a study published in 2002, Norhammar et al. showed that the prevalence of glucose abnormalities, i.e., glucose intolerance or diabetes, in a population of patients hospitalized for acute myocardial infarction was approximately 65%, both when they were discharged from the hospital and 3 months after hospitalization [5].

For postprandial blood glucose, or blood glucose following a post-load oral glucose, the literature demonstrates the importance of this parameter on cardiovascular risk, not only in primary prevention. The Honolulu Heart Program, published in 1987, showed that the 1-h post-load-glucose is predictive of mortality from coronary disease [6]. The Diabetes Intervention Study, in 1996, underscored the role of postprandial blood glucose on cardiovascular diseases [7]. The Chicago Heart Study, published in 1997, showed that the 2-h post-load-glucose was predictive of overall mortality [8]. The analysis of the Whitehall Study, the Paris Prospective Study, and the Helsinki Policemen Study, in 1998, also concluded that the 2-h post-load-glucose was predictive of overall and cardiovascular mortality [9]. In 1997, the Hoorn Study emphasized that the 2-h post-load-glucose is a better predictor of cardiovascular mortality than HbA1c [10]. In 1999, the DECODE (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe) study showed that postprandial blood glucose was associated with an increase in mortality, independently of fasting blood glucose [11]. In 2002, the Framingham Offspring Study lead to the same result [12]. Finally, the Baltimore Longitudinal Study on Aging, published in 2004, showed that impaired glucose tolerance is a greater cardiovascular risk factor than fasting glucose, even if the threshold is lower than 5.5 mmol/l [13].

All of these investigations, from 1987 to today, were grouped in a meta-analysis that included 20 studies and more than 96,000 patients. It was confirmed that post-load-glucose, rather than postprandial blood glucose, was an independent cardiovascular risk factor [14].

Intervention studies have confirmed these epidemiological data. This is true for the DCCT (Diabetes Control and Complications Trial), which showed that in type 1 diabetic subjects on intensive therapy, the number of cardiovascular events decreased by 44% compared to the patients on conventional treatment. However, the difference was not significant because of the low number of events [15]. Nevertheless, the EDIC (Epidemiology of Diabetes Interventions and Complications) study [16], conducted 10 years later in the same population, emphasized that despite the absence of a difference in HbA1c levels between these two groups, cardiovascular mortality and the number of myocardial infarctions were significantly reduced by 50% in the group that had had intensive therapy. The predictive factors were microalbuminuria and HbA1c level at inclusion in the DCCT study. These results constitute indirect evidence that reinforced treatment of hyperglycemia, even over a limited period of time, improves cardiovascular prognosis over the long term and that a "glycemic memory" exists concerning the risk of complications.

In the United Kingdom Prospective Diabetes Study (UKPDS) investigating type 2 diabetic patients, a 1% decrease in HbA1c resulted in a 14% reduction in the risk for myocardial infarction, at the limit of statistical significance. However, this reduction was of 44% in the obese subgroup of patients treated with metformin. A 12% reduction was also noted for the risk of stroke, 16% for the risk of cardiac failure, and 43% for the risk of lower limb arteritis. This last point raises the question of the existence of a more specific relation between hyperglycemia and atherosclerosis of the arteries of the lower limbs compared to other arterial trunks. However, it must be remembered that the diagnosis of arteritis of the lower limbs is operator-dependent and that carotid atherosclerosis can be asymptomatic.

The UKPDS 35 intervention study found a nearly perfect correlation between the HbA1c level and microangiopathy complications, specific to hyperglycemia. Nevertheless, this correlation is at the limit of statistical significance between the HbA1c level and myocardial infarction. Indeed, the risk of myocardial infarction is not negligible, even in patients with a well-controlled diabetes with a HbA1c level of 5.5%, again suggesting that blood glucose is an independent atherosclerosis risk factor, but not a major one, compared to the classical risk factors [17].

The Steno 2 Study was conducted in Denmark in 160 type 2 diabetic patients at very high cardiovascular risk, but without cardiovascular history. These patients presented with a pathological microalbuminuria, whose predictive value for cardiovascular events is well-known. Eighty patients were randomly assigned to each group and seventy-six patients received an
intensive therapy and 73 a conventional treatment until the end of the 8-year follow-up. The primary objective was to evaluate cardiovascular risk, assessed using a composite criterion (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, revascularization with coronary-artery by-pass grafts or percutaneous angioplasty, vascular surgery for arteritis of the lower limbs). The secondary objective was to evaluate the risk for microangiopathy [18].

In both groups, goals were set for glycosylated hemoglobin, total cholesterol and triglyceride levels, as well as for systolic and diastolic blood pressure; however, these goals evolved over the time the patients were included in the study (Table 1).

The intensive treatment regimen was multifactorial. Diet was controlled, with a total daily intake of fat that was less than 30% of the daily energy intake, less than 10% of the daily calorie intake from saturated fatty acids, and a vitamin-mineral supplement containing vitamin C (250 mg/d), D-alpha-tocopherol (100 mg/d), folic acid (400 μg/d), and chrome picolinate (100 μg/d). Physical exercise corresponding to at least 30 min of rapid walking three to five times a week was recommended.

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>Conventional group</th>
<th>Intensive group</th>
</tr>
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<tbody>
<tr>
<td>Systolic BP (mmHg)</td>
<td>&lt; 160 &lt; 135</td>
<td>&lt; 140 &lt; 130</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>&lt; 95 &lt; 85</td>
<td>&lt; 85 &lt; 80</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>&lt; 7.5 &lt; 6.5</td>
<td>&lt; 6.5 &lt; 6.5</td>
</tr>
<tr>
<td>Fasting serum total cholesterol (mmol/l)</td>
<td>&lt; 6.5 &lt; 4.9</td>
<td>&lt; 4.9 &lt; 4.5</td>
</tr>
<tr>
<td>Fasting serum triglycerides (mmol/l)</td>
<td>&lt; 2.2 &lt; 2.0</td>
<td>&lt; 1.7 &lt; 1.7</td>
</tr>
<tr>
<td>Treatment with ACE inhibitor irrespective of BP</td>
<td>No Yes Yes Yes</td>
<td></td>
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<tr>
<td>Aspirin therapy for patients:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- with known ischemia</td>
<td>Yes Yes Yes Yes</td>
<td></td>
</tr>
<tr>
<td>- with peripheral vascular disease</td>
<td>No No Yes Yes</td>
<td></td>
</tr>
<tr>
<td>- without coronary heart disease or peripheral vascular disease</td>
<td>No No No Yes</td>
<td></td>
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BP: blood pressure; ACE: angiotensin converting enzyme.

Patients were expected to stop smoking and were treated with an angiotensin-converting enzyme inhibitor (ACEI); captopril (50 mg, b.i.d.), or an angiotensin II receptor antagonist (“sartan”) if the ACEIs were contraindicated or poorly tolerated. A lipolowering treatment with a statin and/or a fibrate was prescribed, as well as aspirin at 150 mg/d. Finally, the diabetes treatment was either with oral antidiabetic agents, or if unable to maintain glycosylated hemoglobin below 6.5% with a combination of oral antidiabetic agents and NPH insulin at bedtime, or even intensive insulin therapy.

Comparing the percentages of patients who had met the different objectives in each group, it was found that it was easier to treat hypercholesterolemia, high blood pressure, or hypertriglyceridemia, given that HbA1c goal was only reached in 15% of the patients on intensive therapy after 8 years of follow-up. Thus, at the end of the study, the additional benefit of an intensive therapy was – 11 mmHg for systolic blood pressure, – 1.21 mmol/l for total cholesterol, – 0.87 mmol/l for LDL-cholesterol, and only – 7% for HbA1c.

Due to these beneficial differences on the metabolic control, the cardiovascular risk was lowered by 53% in the intensive therapy group, which was highly significant. In addition, the secondary objective was met with a significant reduction in diabetic microangiopathy. The obvious conclusion of this study is that a long-term intervention on multiple risk factors in microalbuminuric type 2 diabetic patients reduces the risk of cardiovascular events by half. However, the importance of blood glucose cannot be individualized in this study.

A meta-analysis performed on seven studies that included 2180 type 2 diabetes patients, treated either with acarbose or placebo, showed a significant reduction in myocardial infarction risk in the group treated with acarbose. These results are very important, with the reserve that data from other investigations should be integrated, notably those from the UKPDS study, which was not included in this meta-analysis [19].

The PROactive (Prospective Pioglitazone Clinical Trial in MacroVascular Events) study, a secondary prevention study, which included 5238 patients with type 2 diabetes who had evidence of macrovascular disease, followed up for 3 years, showed a 16% reduction in the risk of at least one event in the main secondary endpoint, a composite of all-cause mortality, nonfatal myocardial infarction (excluding silent myocardial infarction), and stroke. Treatment with pioglitazone reduced HbA1c by 0.5%, raised HDL-cholesterol by 8.9%, and reduced systolic blood pressure by 3 mmHg and triglycerides by 13.2% [20]. Again in this study, the importance of blood glucose could not be individualized [21].

### Conclusions

Fasting blood glucose is an independent cardiovascular risk factor, but not a major one. Two-hour post-load-glucose, and postprandial glucose, seem more important, especially since it potentiates the other major risk factors.
There is an existing risk as soon as HbA1c rises above 6.2%, whereas the threshold defining “diabetes” was retained based on the risk for microangiopathy and in particular retinopathy.

The meta-analysis published by Coutinho et al. in 1999 [14], which included 20 studies with a total of 95,783 subjects followed up for 12.4 years, concluded that fasting glucose at 1.10 g/l increases the cardiovascular risk by 1.33, compared to fasting glucose below 0.75 g/l, a significant figure. For 2-h post-load-glucose, it increases the risk more sharply, by 1.58, when above 1.40 g/l.

New studies are necessary to determine whether the blood glucose thresholds and goals to meet should be reinforced.

References